

BIOLOGICAL DIFFERENTIATION OF BENIGN AND MALIGNANT GROWTHS*

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ONE phase of an extensive constitutional study under progress in this laboratory has been an investigation of spontaneous neoplasia in the rabbit and, as a result of routine clinical and pathological examinations carried on over a period of years, a considerable series of tumors has been found. Cancers of the breast and of the uterus have occurred with the greatest frequency and have been subjected to more thorough study than the less common tumors of other organs. It is encouraging that in morphology, mode of development and biological characteristics, these growths bear a much closer resemblance to human cancers than do the corresponding tumors under study in other animal species.

A characteristic feature of the breast and uterine cancer is the occurrence of a well defined developmental history (Greene and Saxton 1938,¹ Greene 1939²). They do not arise as a sudden transition of normal cells but, on the other hand, represent the final step in a progressive developmental process during the course of which the primary neoplastic focus passes through successive stages of anaplastic cellular change, local tissue invasion, foreign tissue invasion and eventually metastasis. Transplantation experiments utilizing the anterior chamber of the eye as an inoculation site showed that the tumors could not be transferred to normal animals during stages of anaplastic cellular change or of local tissue invasion but could be transferred to normal animals during the stage of foreign tissue invasion (Greene 1940³). It was, therefore, concluded that anaplastic cellular change or local tissue invasion in the primary growths of these tumors did not constitute evidence of autonomy but rather stages in the development of autonomy, the final attainment of which was only evidenced by foreign tissue invasion.

In contrast to the failure of transfer to normal animals during

* Abstract of paper read at the Stated Meeting of The New York Academy of Medicine, March 2, 1944.

stages prior to foreign tissue invasion, it was found that at such stages the developing tumors could be successfully transplanted to animals bearing spontaneous growths. This finding suggested that special factors were present in the spontaneous hosts but absent in normal animals and the nature of the endocrine changes constantly found in tumor bearing animals indicated that one of these factors might be an abnormal secretion of estrone. It was subsequently found that dependent tumors survived and grew in estrinized animals, whereas early death of the transplants occurred in normal animals used as controls and it was concluded that the constitutional status incident to an abnormal secretion of estrone was one of the factors essential to the continued growth and development of the tumors (Greene 1940⁴).

Cancers of the breast and uterus have been carried for many serial generations in normal rabbits and experimental investigations have been concerned with attempts to alter malignancy and to determine the immunological status of animals during different stages of tumor growth (Greene 1939,⁵ 1940³). The tumors have also been successfully transplanted to foreign species, including guinea pigs, hens, goats, sheep and hogs, by means of the anterior chamber technique (Greene 1941⁶). The tumors receive a blood supply from the alien host and grow progressively. The cells of the transplant, however, are descendants of the original tumor and not derivatives of the foreign species.

The anterior chamber has also been used for the heterologous transplantation of mouse tumors and it has been found that in this species tumors undergo the same biological phases of dependency and autonomy observed in the development of rabbit cancer.

It has also been possible to transplant human tumors to lower species using this route of inoculation (Greene 1942,⁷ 1944⁸). A considerable series of human tumors have been tested and it has been found that successful transplantation to normal animals could only be performed after the occurrence of foreign tissue invasion and it was concluded that, in human as in rabbit tumors, this stage marks the attainment of autonomy.

An interpretation of the significance of the capacity of cancer tissue to grow in alien hosts necessitated a more accurate definition of the limits of heterotransplantability and a series of experiments was instituted to determine whether or not this power was shared by other tissues. Benign tumors, normal adult tissue and normal embryonic tissue

(Greene 1943⁹) have been tested with respect to this property as well as to the ability to survive and grow in other environments and the results are presented in the accompanying chart.

TRANSFER

<i>Tissue</i>	<i>Autologous</i>	<i>Homologous</i>	<i>Heterologous</i>
Normal Adult	+	+	—
Normal Embryonic	+	+	+
Benign Tumor	+	—	—
Cancer	+	+	+

The property of heterologous transplantability accents the relationship between cancer and embryonic tissue and suggests the possession of a common attribute that differentiates them biologically from other normal and pathological tissue states.

The primary conclusions indicated by the findings described in this abstract are first, that the rabbit cancers are not simply local tissue diseases but, on the other hand, represent local manifestations of a generalized constitutional disorder and, second, that in the rabbit the primary neoplastic focus is not a cancer and that before becoming a cancer it must undergo a process of progressive evolutionary development. Development to cancer will not take place in normal animals but is dependent on a special constitutional status which may be evoked experimentally by the administration of estrogenic substances. Both human and mouse cancers undergo a similar developmental course in their advance to cancer and in all of the species studied this course is characterized by dependent and autonomous phases.

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